Infectious Diseases Diagnosis & Treatment

Sanker R, et al. Infect Dis Diag Treat 7: 208.

www.doi.org/ 10.29011/2577- 1515.100208

www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Research Article

A Retrospective Observational Study on The Effect of Steroid Use in Covid-19 Patients

Rakesh Sanker*, Srinivasa Rao Polumuru, Pavan Shrivastava, Lexy Vijayan, Mohamed Soliman, Salini Sasidharan, Keerthana Kalliat

NMC Specialty Hospital, Al Nahda, Dubai, UAE

***Corresponding author:** Rakesh Sanker, Principal Investigator, Specialist in Internal Medicine, NMC Specialty hospital, Dubai, UAE.

Citation: Sanker R, Polumuru SR, Shrivastava P, Vijayan L, Soliman M, et al., (2023) A Retrospective Observational Study on The Effect of Steroid Use in Covid-19 Patients. Infect Dis Diag Treat 7: 208. DOI: 10.29011/2577-1515.100208

Received Date: 7 March 2023; **Accepted Date:** 14 March 2023; **Published Date:** 20 March 2023

Abstract

Background and objectives: Dexamethasone received worldwide coverage after publishing of the Recovery trial. In view of this, we performed a retrospective observational study on the effect of steroids in coronavirus disease 2019 (COVID-19) infection.

Methods: A total of 62 patients of COVID-19 were treated with steroids- steroid group (SG), and 49 patients of COVID-19 were given standard of care treatment (SOC). Primary objectives analyzed: 28-day mortality, number of ventilator days, and number of days on oxygen support. Secondary objectives: Length of Intensive Care Unit (ICU) stay, length of hospital stay, and morbidities.

Results: The primary objective of 28-day mortality in COVID-19 Acute Respiratory Disease Syndrome (ARDS) - critical + severe patients - were lower in those in SG (21.6%) than in SOC (33.3%). The median number of ventilator days in SG was 7, and it was 9 in SOC. The mean number of days on oxygen support in ARDS critical + severe patients was 5.5±2.2 days for those in SG compared with 8.3±1.0 days for those with SOC ($p<0.05$). The secondary objective of the number of mean ICU days in ARDS critical + severe for SG vs. SOC patients was 9±6.1 vs. 9.5±5.8, which appeared to trend towards a shorter ICU stay in SG patients.

Interpretation and Conclusions: The number of days on oxygen support in SG patients was less than for SOC patients and was statistically significant. The other outcomes showed a lower mortality rate, and lower number of ventilator days, in severe and critical SG patients. Although not statistically significant, this showed a general trend towards the treatment benefit of steroids.

Keywords: Acute Respiratory Distress Syndrome (ARDS); Covid-19; Dexamethasone; Methylprednisolone; Mortality; Steroids; Ventilator days.

Introduction

On the 1st of August, 2020, the United Nations reported that the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first reported in December 2019 in Wuhan, China, had spread all over the world and had infected over 17 million people and resulted in over 650,000 deaths, with no end in sight to this public health crisis [1]. Of these cases, approximately 80% were considered to be mild to moderate, 13.8% were severe, and approximately 6.1% cases had progressed to a critical stage requiring intensive care [2]. As of March 2020, the World Health Organization (WHO) reported mortality rates ranging from 0.2% in Germany to approximately 7.7% in Italy with a mean of 3.7% around the world [3,4]. In the United Kingdom, the case fatality rate was approximately 26% in patients who received ward care only and was 37% in patients who were on invasive ventilation [5].

ARDS in COVID-19

An increase in acute phase reactants in patients with COVID-19 (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid A, and ferritin) point to brisk immune activation. Cytokines are integral to COVID-19 pathogenesis, some of which are beneficial (type-I interferon and interleukin-7), whereas others appear to be harmful (interleukin-1ß, Interleukin-6 (IL-6), tumor necrosis factor (TNF-a)). Moderate levels of cytokines, such as CRP, ferritin, D-dimer, alanine transaminase (ALT), and lactate dehydrogenase (LDH), have been observed

in severe ARDS, whereas in the 'cytokine storm', very high levels of IL-6, ferritin, and CRP have been observed, leading to ARDS, disseminated intravascular coagulation, or multiple organ failure. This cytokine storm syndrome results in high morbidity and mortality [6-10]. Hyaline membrane formation, pneumocyte atypical hyperplasia, and platelet–fibrin thrombi in small arterial vessels, which are consistent with coagulopathy, and are other unique pathophysiological features of COVID-19 ARDS [11].

The mortality arising from COVID-19 ARDS has been shown to be much higher (26–61.5%) than the mortality due to typical ARDS arising from other conditions (35.3–40%) [12-13]. In other closely related viral infections, such as SARS-CoV-1, Middle East Respiratory Syndrome (MERS) coronavirus, and influenza, viral replication peaks in the second week, whereas in SARS-CoV-2, viremia occurs early (in the first week) and decreases subsequently [14].

Steroids in ARDS

ARDS of any etiology have high rates of morbidity and mortality worldwide. Incidence of ARDS in 459 ICUs worldwide, according to Bellani et al., in 2016 was approximately 10.4%, and approximately a quarter of these required mechanical ventilation. The overall hospital mortality from ARDS ranged from 34.9% for mild ARDS to 46.1% for severe ARDS.12 Similar statistics for mortality (38.5%) was found in a previously conducted study in Washington, which surveyed 21 hospitals, thus confirming the profoundly serious nature of this disease [15].

In trials of corticosteroids used in ARDS conducted prior to 2005, the use of steroids was not based on any set criteria, such as type, dosage, duration, or severity. Therefore, the results were not consistent across studies; hence, the use of corticosteroids in ARDS remained uncertain [16,17].

A negative result was found in a systematic review and meta-analysis of 6548 patients with influenza pneumonia where mortality was higher in the steroid group [18].

In a multicenter randomized controlled trial (RCT) conducted in Spain across five years and published in March 2020 of enrolled patients with moderate to severe ARDS, the steroid group was given dexamethasone (20 mg from day 1 to day 5 and tapered off to 10 mg from days 6 to 10). Both the steroid and non-steroid control groups were ventilated with lung-protective mechanical ventilation. The mean number of ventilator-free days was higher in the dexamethasone group than in the control group (between-groups, difference was 4.8 days, $p<0.0001$) suggesting a benefit. In addition, the 60-day mortality was favorable towards the steroid group (21% vs. 36%, $p=0.0047$ in the control group) [19]. This recent study gave hope of steroids, with lung-protective mechanical ventilation, as a treatment option in ARDS.

Steroid Use in COVID-19 ARDS

In January 2020, at the break of the pandemic, the interim guidance from the WHO explicitly stated that unless indicated for another reason, corticosteroids may not be routinely used to treat ARDS due to the possible complications and lack of effectiveness [20]. Soon after, in February 2020, Russel et al. found four studies with conclusive data, all indicating the harmful effects of steroids. It was postulated that steroids not only suppress lung inflammation but also hinder the immune response and pathogen clearance. Furthermore, the use of steroids brought about secondary infections and complications in survivors. From all the above evidence, Russel et al. concluded that steroids should not be used for treatment of COVID-19 outside of a clinical trial [21].

Subsequently, a multicentric trial in June 2020 with intravenous methylprednisolone (40 mg/12 h for 3 days, 20 mg/12 h for 3 days) showed a beneficial effect with a lower risk of ICU admission (8% vs. 28%, $p=0.047$), lower NIV (6% vs. 10%, ns) and death (20% vs. 18%, ns), and a 50% lower risk of a composite adverse outcome [22].

An early, short course of methylprednisolone (0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days) in a multicenter health system in Michigan in March 2020 concluded that there was a reduction in length of hospital stay (5 vs. 8 days, $p<0.01$), which thus reduced escalation of care and improved clinical outcomes [23].

In the CODEX trial in ICUs in Brazil, moderate to severe COVID-19 ARDS patients were administered dexamethasone (20 mg for 5 days, 10 mg for 5 days). Results showed a significant increase in the number of ventilator-free days, suggesting a benefit (6.6 vs. 4, $p=0.04$). However, for the 28-day mortality, there were no significant differences [24].

The REMAP-CAP study was done with a 7-day course of intravenous hydrocortisone (50 mg or 100 mg every 6 hours) with a 93% probability of benefit based on improvement in organ support–free days within 21 days [25].

The RECOVERY trial published in July 2020 provided conclusive evidence that treatment with dexamethasone (6 mg once daily for up to 10 days) reduced death by 1/3rd in ventilated patients and by 1/5th in patients on oxygen support, and no benefit among patients who did not receive or require respiratory support. The trial included 2104 patients in the steroid group and 4321 patients in the usual care group. The primary outcome of 28-day mortality for all patients was highly significant (22.9% vs. 25.7%, $p<0.001$), with maximum benefit noticed in those on invasive ventilation (29.3% vs. 49.4%) and in those on oxygen support (23.3% vs. 26.2%). The secondary outcomes of length of hospital stay and progression to mechanical ventilation were also benefited

by dexamethasone [14].

Our Aim

As discussed above, trials prior to the Recovery trial for steroids in COVID-19 ARDS tended towards a benefit but did not result in a clear conclusion due to the heterogeneity in type, dosing, and timing of steroids. The Recovery trial, however, with its large sample size and well-designed trial showed conclusive evidence that dexamethasone is beneficial for treatment of COVID-19 ARDS. With this knowledge, we planned to do a retrospective observational analysis of the COVID-19 patients at our hospital. The patients were classified based on the Berlin criteria of ARDS severity: mild (200-300), moderate (100-200), severe (<100), and critical (if patient was on high flow nasal oxygen (HFNO)/ non-invasive ventilation (NIV)/ mechanical ventilation (MV)) [26]. The patients were divided into two groups: the steroid group (SG) and standard of care (SOC) group.

Methods

Study Design

We conducted a retrospective observational study at NMC Specialty Hospital, Dubai, a 100 bed, tertiary care hospital, over a period of 5 months from March 2020 to July 2020 during the first wave of COVID-19. Hospitalized patients were included in the study if they fulfilled the followingcriteria:

a) a positive RT PCR test (reverse transcriptase polymerase chain reaction),

b) suspected COVID-19 based on clinical and radiological features despite a negative RT PCRtest,

c) bilateral infiltrates and/or interstitial opacities on chest X-ray,

d) PaO2/FiO2 (P/F) ratio of <200 as per Berlin criteria of moderate ARDS,

e) high inflammatory markers (CRP, ferritin)

f) received any type of corticosteroids during the period of study.

Of the 256 COVID-19 patients admitted to this hospital, 111 patients fulfilled the inclusion criteria and were divided into two groups: 62 patients were treated with steroids and were designated as the steroid group (SG). The other 49 patients were not treated with steroids but received standard of care treatment (SOC). Both groups were treated in accordance with the national guidelines at that time with the addition of steroids in the SG.

Patient data were collected from various departments, namely the medical records department, laboratory, and in-patient pharmacy. This included demographic data and comorbidities, clinical signs and symptoms and severity at presentation, laboratory and radiological data, in-patient treatment, data on steroids and other supportive medications used.

This study has been approved by the Dubai Scientific Research Ethics Committee (DSREC), Dubai Health Authority, dated 17th September 2020 (Ref: DSREC- 09/2020_22).

Outcome Measures

The primary objectives of the study were to compare the following outcome measures in the SGand SOC:

1. 28-day mortality - number of patients who died during hospital day or in the 28-day period (whichever came earlier) following treatment.
2. Number of ventilator days - number of ventilator days following the start of intubation and mechanical ventilation until the last extubation. Ventilator days for reintubated patients are counted as a continuation until final extubation.
3. Number of days on oxygen support - number of days from when oxygen was first started until it was weaned off to 3L of oxygen support or a P/F ratio of >300.

The secondary objectives involved comparing the following outcome measures in the SG and SOC groups:

1. Length of stay in the ICU,
2. Length of stay in the hospital,
3. Morbidities in terms of cardiac, renal, and neurological complications.

Other secondary objectives included:

1. To enumerate the type of steroid used, dosage, and duration in the SG
2. To examine other supportive medications used in both groups.

Statistical Analysis

The data collected from electronic records were compiled in an Excel worksheet. Descriptive analysis was performed for demographics and clinical and laboratory records. The mean/ median, standard deviation, and percentages are reported in the tables below. To investigate the association between SG and SOC to mortality (dead/alive) and morbidity, the Chi square test was used. Analysis of outcome measures with continuous variables, such as ventilator days, oxygen days, ICU days, and hospital days, was performed using the Independent T test for mean duration, and Mann Whitney U test for median duration. All analyses were performed using IBM SPSS (version 27.0; IBM Corp., Armonk, NY, USA). A two-sided p-value of <0.05 was considered as statistically significant.

Results

Demographics and Comorbidities - Table 1:

In both groups, most patients were in the 40–60 age range with the SG having a mean (±SD) age of 50.4±10.4 and the SOC having a mean (±SD) age of 47.2±11. Both groups were made up of a much larger percentage of males with 90.3% in SG and 83.7% in SOC. A variety of nationalities were treated, the majority being of South Asian descent (Indian, Pakistani and Bangladeshi), which made up 66.1% and 67.3% of patients in SG and SOC, respectively (Table 1).

DEMOGRAPHICS	STEROID TREATMENT(N=62) N (%)	STANDARD OF CARE(N=49) N (%)
AGE RANGE		
<30	2 (3.23%)	4 (8.16%)
30-40	10 (16.13%)	7 (14.29%)
40-50	14 (22.58%)	18 (36.73%)
50-60	23 (37.1%)	11 (22.45%)
>60	13 (20.97%)	9 (18.37%)
MEAN (SD)	50.35 (10.37)	47.16 (10.96)
GENDER		
MALE	56 (90.32%)	41 (83.67%)
FEMALE	6 (9.68%)	8 (16.33%)
NATIONALITY		
INDIAN	30 (48.39%)	23 (46.94%)
PHILIPPINE	9 (14.52%)	7 (14.29%)
PAKISTANI	9 (14.52%)	4 (8.16%)
BANGLADESHI	2 (3.23%)	6 (12.24%)
MIDDLE EAST*	8 (12.9%)	4 (8.16%)
OTHERS†	4 (6.45%)	5 (10.2%)
COMORBIDITIES		
DIABETES MELLITUS	26 (41.94%)	19 (30.65%)
HYPERTENSION	27 (43.55%)	11 (17.74%)
CORONARY ARTERY DISEASE	5 (8.06%)	4 (6.45%)
OTHERS‡	19 (30.65%)	8 (12.9%)
NO COMORBIDITIES	18 (29.03%)	25 (40.32%)

* Includes Lebanese, Sudanese, Palestinian, Egyptian
† Includes German, British, Indonesian, Nepali, Sri Lankan
‡ Includes Asthma, Hlp, Hypothyroidism, Obesity, Copd, Ra, Pregnancy

Table 1: Demographics and Comorbidities.

Comparison and Severity of Disease -Table 2 and Figure 3:

The SG consisted of more critical or severe ARDS patients (82.3%), whereas only 24.5% of patients in SOC presented the same. This observation confirmed that SG consisted of patients with a more serious disease compared to SOC, which consisted of mild and moderate cases (Table 2).

INDICATION	STEROID GROUP (N=62)N (%)	STANDARD OF CARE GROUP(N=49) N (%)
ARDS CRITICAL*	33 (53.23%)	6 (12.24%)
ARDS SEVERE	18 (29.03%)	6 (12.24%)
ARDS MODERATE	8 (12.9%)	31 (63.27%)
ARDS MILD	2 (3.23%)	6 (12.24%)
ARDS NIL	1 (1.61%)	0 (0%)
* SUB-ANALYSIS OF ARDS CRITICAL + SEVERE: STEROID GROUP (N=51, 82.26%) AND CONTROL GROUP (N=12, 24.48%)		

Table 2: Clinical Severity.

Figure 3(a) shows the lab parameters of inflammation and coagulation markers (e.g., CRP, ferritin, D-dimer, and IL-6), which are direct indicators of COVID disease severity. The mean (±SD) CRP value in SG was 147.2±93.7 versus 103.1±66.0 in SOC with statistical significance ($p<0.05$). Similarly, statistical significance was also achieved for the mean D-dimer values (SG= 1079±1512.3 and SOC= 597.5±843.3). Although the mean values for ferritin and IL-6 did not achieve statistical significance, the values were higher in SG than in SOC for both markers.

The different levels of severity based on chest X-ray were graded as unilateral lobar pneumonia, bilateral pneumonia, and worsening of bilateral pneumonia. In SG, 41 (66.1%) patients had worsening of bilateral pneumonia compared with 17 (34.7%) in SOC ($p<0.05$). These laboratory and radiological values measured during the worsening of symptoms clearly points to the more severe nature of the disease of SG when compared to that of SOC (Figure 3(b)).

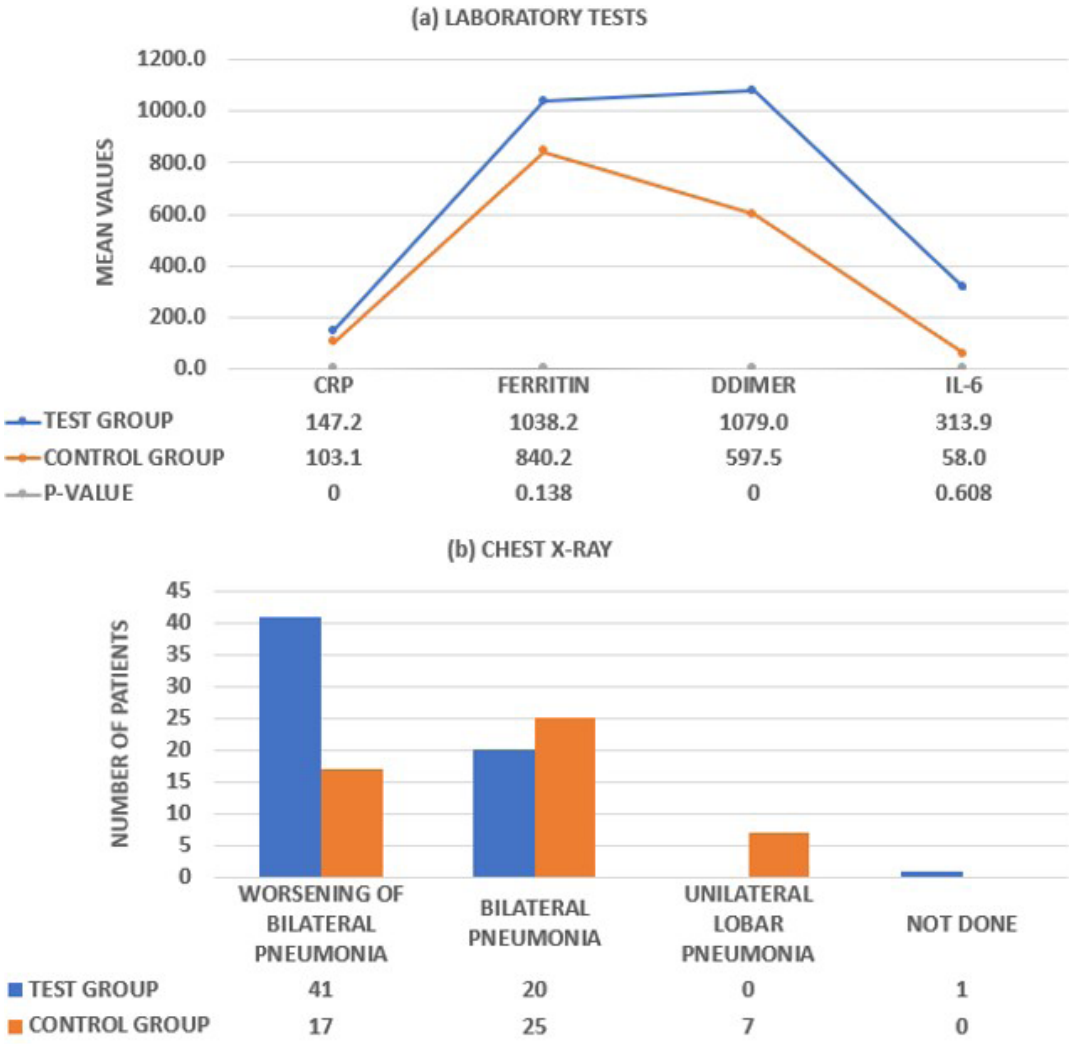

FIGURE 3. SEVERITY BASED ON LABORATORY AND RADIOLOGY

Primary and Secondary Outcomes - Table 4:

As patients are sub-categorized by ARDS severity, outcome measures were examined individually for each ARDS category. Furthermore, in all outcome measures, a combined value of ARDS critical + severe cases were taken, which provided a more meaningful analysis (Table 4).

Primary Objectives:

28-day mortality- Of the 62 patients, there were 11 deaths (17.7%) in SG, whereas there were 4 deaths (8.2%) of the 49 patients in SOC. However, when analyzed by severity, the mortality of patients for ARDS critical + severe, was lower in SG- 11 out of 51 patients (21.6%) than in SOC- 4 out of 12 patients (33.3%). Although this did not achieve statistical significance, it does show a trend towards reduced mortality in the SG.

Number of ventilator days- A total of 25 patients in SG were placed on ventilators compared with 5 patients in SOC for the ARDS critical category. In SG patients, the median ventilator days was 7, whereas for SOC, the median was 9. The trend showed a reduction of ventilator days in SG, although statistical significance was not achieved due to the small sample size.

Number of days on oxygen support- In the SG patients, the mean (±SD) oxygen days for ARDS critical + severe category was 5.5±2.2 days, compared with 8.3±1.0 days in SOC patients ($p<0.05$). Similarly, statistical significance was achieved for all patients for days of oxygen support (34 days in SG vs. 44 days in SOC). These results show that treatment with steroids caused a reduction in the number of days on oxygen support.

Secondary Objectives:

Number of ICU days: The mean (±SD) number of ICU days in ARDS critical + severe in SG vs. SOC patients was 9±6.1 vs. 9.5±5.8 respectively, with $p=0.788$, showing a trend towards shorter ICU stay in the SG. However, when total patients were considered, the mean (±SD) was found to be slightly more in the SG (8.9±6.0 vs. 8.8±5.6, $p=0.953$).

Number of days in the hospital: The mean (±SD) was higher in SG (14.7±7.6) than in SOC (10.5±4.7) with $p<0.05$. This result was anticipated because the SG consisted of more critical and severe patients, so a longer hospital stay was expected.

Number of days from onset to admission and worsening: These parameters compared the progression of disease in both groups. In SG and SOC, the mean days from onset to admission were 6.7±5.0 and 6.8±3.6, respectively. From onset to worsening, the mean days for SG were 8.8±5.1, and it was 7.7±3.5 for SOC. These results are similar to those observed in other studies [14].

Morbidities: During treatment and at discharge, patients were evaluated for any morbidities that may have occurred. In SG, a total of 14 cases of morbidities were observed versus 5 cases in SOC. In SG, the highest percentage of morbidities were due to nephrological complications (28.6%), whereas in SOC, sepsis and cardiovascular complications accounted for 80% of morbidities.

PRIMARY OUTCOMES			
MORTALITY	STEROID GROUP	STANDARD OF CARE GROUP	P-VALUE
	N (%) OR MEAN (SD) OR MEDIAN (SD)	N (%) OR MEAN (SD) OR MEDIAN (SD)	
ARDS CRITICAL + SEVERE	11 (21.57%)	4 (33.33%)	0.457
ARDS CRITICAL	11 (33.33%)	4 (66.67%)	0.18
ARDS SEVERE	0 (0%)	0 (0%)	N/A
ARDS MODERATE	0 (0%)	0 (0%)	N/A
ARDS MILD	0 (0%)	0 (0%)	N/A
ARDS NIL	0 (0%)	0 (0%)	N/A
TOTAL CASES	11 (17.74%)	4 (8.16%)	0.143
NUMBER OF VENTILATOR DAYS			
ARDS CRITICAL + SEVERE	7 (6.75)	9 (6.87)	0.978
ARDS CRITICAL	7 (6.75)	9 (6.87)	0.978
ARDS SEVERE	0 (0)	0 (0)	N/A
ARDS MODERATE	0 (0)	0 (0)	N/A
ARDS MILD	0 (0)	0 (0)	N/A
ARDS NIL	0 (0)	0 (0)	N/A
TOTAL CASES	7 (6.75)	9 (6.87)	0.978
NUMBER OF DAYS ON OXYGEN SUPPORT			
ARDS CRITICAL + SEVERE	5.54 (2.21)	8.28 (0.95)	P<0.05
ARDS CRITICAL	4.87 (1.88)	8 (0)	0.162
ARDS SEVERE	5.83 (2.33)	8.33 (1.03)	P<0.05

ARDS MODERATE	3.85 (0.89)	7.06 (1.80)	P<0.05
ARDS MILD	3 (0)	5.17 (1.72)	0.297
ARDS NIL	0 (0)	0 (0)	N/A
TOTAL CASES	5.12 (2.11)	7 (1.86)	P<0.05
SECONDARY OUTCOMES			
ICU DAYS			
ARDS CRITICAL + SEVERE	9 (6.06)	9.54 (5.82)	0.788
ARDS CRITICAL	10.31 (6.6)	11.5 (7.06)	0.691
ARDS SEVERE	6 (3.08)	7.2 (3.11)	0.467
ARDS MODERATE	4 (0)	6 (4.58)	0.742
ARDS MILD	0 (0)	0 (0)	N/A
ARDS NIL	0 (0)	0 (0)	N/A
TOTAL CASES	8.9 (6.04)	8.78 (5.61)	0.953
NUMBER OF DAYS OF HOSPITAL STAY			
ARDS CRITICAL + SEVERE	15.84 (7.84)	13.75 (7.13)	0.402
ARDS CRITICAL	17.82 (8.69)	14.67 (6.80)	0.407
ARDS SEVERE	12.22 (4.16)	12.83 (7.98)	0.808
ARDS MODERATE	10.5 (3.07)	9.87 (2.90)	0.593
ARDS MILD	5.5 (0.70)	7 (2.36)	0.432
ARDS NIL	12 (0)	0 (0)	N/A
TOTAL CASES	14.76 (7.6)	10.47 (4.68)	P<0.05
MORBIDITIES			
NEPHROLOGICAL COMPLICATIONS*	4 (28.57%)	1 (20%)	N/A
SEPSIS	2 (14.28%)	2 (40%)	N/A
PULMONARY COMPLICATIONS†	2 (14.28%)	0 (0%)	N/A
HEMATOLOGICAL COMPLICATIONS‡	2 (14.28%)	0 (0%)	N/A
CARDIOVASCULAR COMPLICATIONS§	1 (7.14%)	2 (40%)	N/A
NEUROLOGICAL COMPLICATIONS**	1 (7.14%)	0 (0%)	N/A
OTHERS††	2 (14.28%)	0 (0%)	N/A
TOTAL CASES	22.58%	10.20%	N/A
NUMBER OF DAYS FROM ONSET TO ADMISSION			
ARDS CRITICAL + SEVERE	6.76 (5.32)	5.83 (3.35)	0.565
ARDS CRITICAL	6.12 (2.82)	3.67 (1.50)	0.047
ARDS SEVERE	7.94 (8.12)	8 (3.34)	0.987
ARDS MODERATE	6.87 (3.04)	6.58 (3.34)	0.823
ARDS MILD	6 (2.82)	9.5 (4.92)	0.392
ARDS NIL	7 (0)	0 (0)	N/A

TOTAL CASES	6.76 (4.94)	6.75 (3.64)	0.997
NUMBER OF DAYS FROM ONSET TO WORSENING OF SYMPTOMS			
ARDS CRITICAL + SEVERE	8.74 (5.56)	7.5 (4.03)	0.468
ARDS CRITICAL	8.18 (3.21)	5.17 (2.85)	0.039
ARDS SEVERE	9.78 (8.34)	9.83 (3.81)	0.988
ARDS MODERATE	9.37 (2.77)	7.29 (3.15)	0.097
ARDS MILD	6.5 (2.12)	10 (4.24)	0.322
ARDS NIL	10 (0)	0 (0)	N/A
TOTAL CASES	8.77 (5.14)	7.67 (3.54)	0.205

* NEPHROLOGICAL COMPLICATIONS- AKI, HEMODIALYSIS, HIGH CREATININE, PROLONGED URINARY CATHETERIZATION.

† PULMONARY COMPLICATIONS- TRACHEOSTOMY, PNEUMOTHORAX, MRSA PNEUMONIA, PULMONARY AV SHUNT.

‡ HEMATOLOGICAL COMPLICATIONS- THROMBOCYTOPENIA, HYPOCALCEMIA, HYPOKALEMIA.

§ CARDIOVASCULAR COMPLICATIONS- MYOCARDITIS, CIRCULATORY SHOCK.

** NEUROLOGICAL COMPLICATIONS- SUB ARACHNOID HEMORRAGE.

†† OTHERS- HEPATITIS, PREGNANCY.

Table 4: Primary and Secondary Outcomes.

Steroids - Type, Duration, and Dosage - Figure 5:

In this study, three steroids were used: Solumedrol (methylprednisolone), dexamethasone and hydrocortisone (Figure 5). Solumedrol was more frequently used (50.8%, 33 patients), followed by dexamethasone (44.6%, 29 patients), with hydrocortisone being least used (4.6%, 3 patients). The average duration of steroid use was 7.64 days for Solumedrol, 6.5 days for dexamethasone, and 2 days for hydrocortisone. For Solumedrol, 80 mg was the most common starting dose (87.9% of patients), followed by 70 mg in 6.1%, and 60 mg in 6.1%. Dexamethasone was used in a starting dose of 20 mg in 51.7% of patients and either 8 mg or 6 mg in 34% of patients. All 3 patients who received hydrocortisone were given the starting dose of 300 mg. In all patients, the steroid dosage was tapered off.

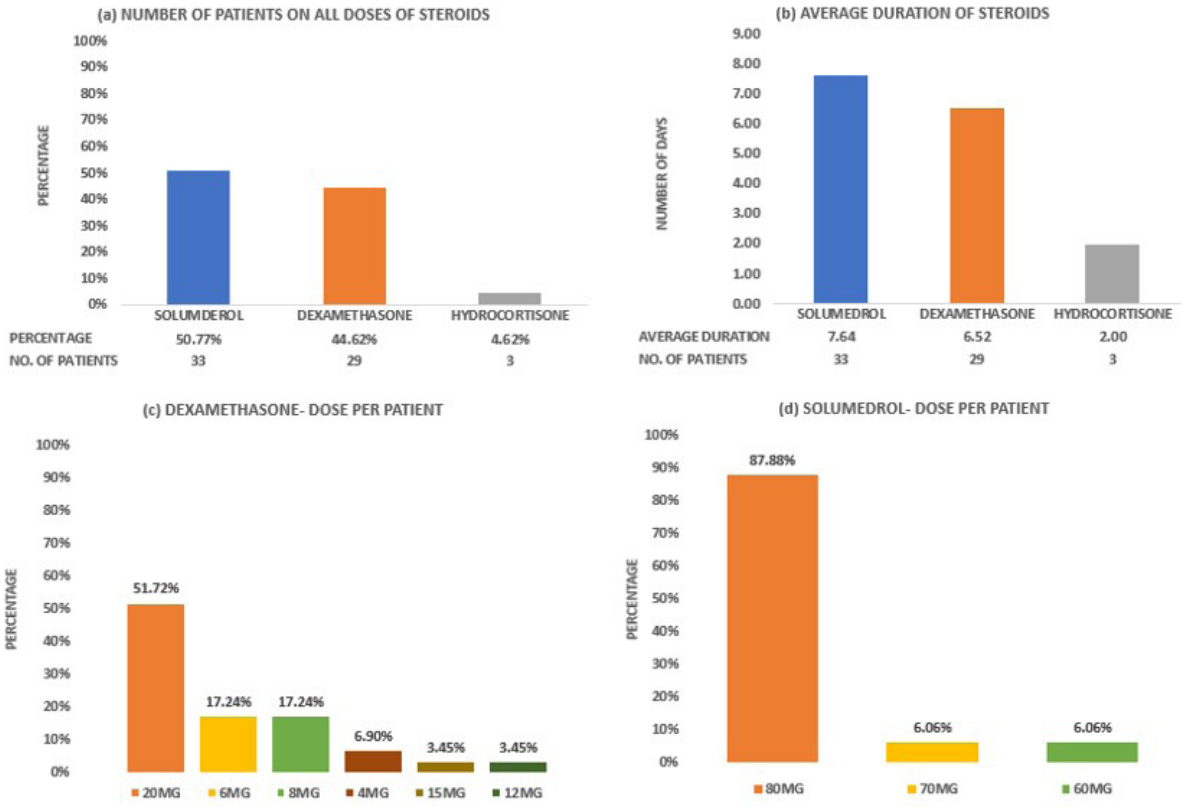

FIGURE 5. STEROIDS USED- TYPES, DURATION AND DOSAGES

Other Medications - Table 6:

The supporting medications included antibiotics, antivirals, anticoagulants, and monoclonal antibodies. Some of these medicines were used either alone or in combination. The most common antibiotic used in SG was cefepime (29.2%), whereas in SOC it was ceftriaxone (46.8%).Hydroxychloroquine sulfate was the most frequently used antiviral in both SG (95.2%) and SOC (98%). Two types of anticoagulants, Clexane (enoxaparin) and Arixtra (fondaparinux), were used. Clexane was further subcategorized into the different dosages administered with 0.6 mg twice daily (BD) used for 42% of those in SG. In SOC, Clexane at 0.4 mg once daily (OD) was usedin 54.35% of cases. Finally, monoclonal antibodies or Actemra (tocilizumab) was used for treatment in 25.8% of patients in SG and 4.1% of patients in SOC (Table 6).

MEDICATIONS ADMINISTERED	STEROID TREATMENT	STANDARD OF CARE
	N (%)	N (%)
ANTIBIOTICS*		
CEFEPIME	28 (29.17%)	9 (14.52%)
MEROPENEM	17 (17.71%)	3 (4.84%)
CEFTRIAXONE	10 (10.42%)	29 (46.77%)
MOXIFLOXACIN	8 (8.33%)	11 (17.74%)
PIPERACILLIN TAZOBACTAM	7 (7.29%)	0 (0%)
TEICOPLANIN	6 (6.25%)	1 (1.61%)
FLUCONAZOLE	5 (5.21%)	0 (0%)
ERTAPENEM	4 (4.17%)	2 (3.23%)
VANCOMYCIN	3 (3.13%)	2 (3.23%)
LINEZOLID	3 (3.13%)	3 (4.84%)
CEFTAROLINE	2 (2.08%)	2 (3.23%)
CAPSOFUNGIN	1 (1.04%)	0 (0%)
ANIDULAFUNGIN	1 (1.04%)	0 (0%)
LEVOFLOXACIN	1 (1.04%)	0 (0%)
ANTIVIRALS		
HYDROXYCHLOROQUINE SULPHATE	59 (95.16%)	48 (97.96%)
LOPINAVIR+RITONAVIR	55 (88.71%)	46 (93.88%)
FAVIPIRAVIR	20 (32.26%)	3 (6.12%)
ANTICOAGULANTS		
CLEXANE 0.6MG BD	26 (41.94%)	4 (8.7%)
CLEXANE 0.4MG OD	23 (37.1%)	25 (54.35%)
CLEXANE 0.6MG OD	5 (8.06%)	3 (6.52%)
CLEXANE 0.4MG BD	4 (6.45%)	14 (30.43%)
CLEXANE 0.8MG BD	3 (4.84%)	0 (0%)
ARIXTRA 2.5MG OD	1 (1.61%)	0 (0%)
MONOCLONAL ANTIBODIES		
ACTEMRA (TOCILIZUMAB)	16 (25.81%)	2 (4.08%)
* Antibiotics Were Used at The Time of Worsening of The Disease		

Table 6: Other Medications.

Discussion

The data for this study was collected during the first wave of the COVID-19 pandemic from March to July 2020 and compiled in the form of a retrospective observational study. The number of patients in both the groups was not evenly matched (62 vs. 49) because the steroids were used more frequently, in addition to standard of care, after the preliminary results of the recovery trial were published in June. Furthermore, the two groups were not evenly matched in severity; SG consisted of more ARDS critical and severe cases, whereas SOC contained mild to moderate cases. Additionally, the laboratory (CRP, ferritin, D-dimer, and IL-6) and radiology (chest X-ray) results for severity (Table 2 and Figure 1) showed that SG patients presented in a more severe condition compared to SOC patients. Comorbidities, such as diabetes mellitus, hypertension, and coronary artery disease, were present either alone or in combination in 93.5% of patients in SG and 54.8% in the SOC group. Therefore, we can concur that patients in the SG would have shown worse outcomes had a treatment intervention - in this case, steroids, not been administered.

In COVID-19, the mortality and morbidity of the disease is dependent on the severity of ARDS. Therefore, we undertook a sub-analysis of a combined value of ARDS critical + severe, in addition to the total, for all outcome measures and compared between the two groups. The total 28-day mortality was observed to be higher in SG than in SOC (17.7% vs. 8.1%). This outcome measure is only meaningful for severe and critical cases; thus, by comparing ARDS critical + severe in both groups, the trend towards a lower mortality rate was observed in SG, despite not reaching statistical significance (21.6% vs. 33.3%, p=0.457). In the second primary outcome, the number of ventilator days showed a smaller median (7 vs. 9, p=0.978), showing a trend towards a benefit of steroids in intubated patients. The third primary outcome examined was the number of days on oxygen support. Patients who were on MV were excluded, as were the mild category. The groups who were on oxygen support, ARDS severe and ARDS moderate, and the total were compared between the two groups. Treatment with steroids caused a reduction in oxygen days (5.5 vs. 8.3, $p<0.05$) which was statistically significant. Regarding statistical significance in ARDS severe, moderate and total, the steroids had a beneficial effect on reducing the number of days on oxygen support.

The secondary objective of ICU days and in-hospital days were higher in SG than in the SOC group (8.9 vs. 8.78 and 14.7 vs. 10.5, respectively). This result was anticipated because the SG consisted of more critical and severe patients, thus a longer hospital stay was expected. But when sub analysis of ICU days in ARDS critical + severe were compared for SG vs. SOC patients (9±6.1 vs. 9.5±5.8) , it appeared to trend towards a shorter ICU stay in SG patients.

The number of days from onset of symptoms to admission and those from onset to worsening were similar to those of other studies. Our results are also in congruence with the observation that COVID-19 symptoms worsen at the end of the first week.

The types and dosage of steroids used were heterogeneous; however, the duration of treatment was consistent across types. Solumedrol (methylprednisolone) dosage was administered in accordance with the guidelines for a moderate dosage (0.5 to 1 mg/kg/day), 80mg per day was given in 50.8% in our study, the other doses being 70mg and 60mg. The results of a composite of the three doses of Solumedrol(methylprednisolone) used in our study, for primary and secondary outcomes, were favorable and comparable with the following two studies. The Michigan trial in March 2020, with a short course methylprednisolone (0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days), as well as a multicentric trial in June 2020 with intravenous methylprednisolone (40 mg/12 h for 3 days, 20 mg/12 h for 3 days) showed a statistically significant reduction in hospital days, a lower risk of ICU admission, lower NIV, death, and lower risk of a composite adverse outcome [22,23].

Dexamethasone was used in a higher dose of 20 mg in a higher number of patients (56%) in comparison to the recovery trial dosage of 6 mg. The CODEX trial in ICUs in Brazil, treated moderate to severe COVID-19 ARDS patients with dexamethasone (20 mg for 5 days, 10 mg for 5 days) and there was a positive benefit for the number of ventilator-free days, though for the 28-day mortality, there was no significant benefit [24]. In comparison with recovery trial which used dexamethasone 6mg daily, in our study 6mg was administered in only 34%. Recovery trial of July 2020 conclusively showed improvement in mortality, reduction in mechanical ventilation and length of hospital stay with 6mg dexamethasone [14]. The results of composite of different doses of dexamethasone used in our study, showed a benefit for the primary outcome of 28 day mortality, number of oxygen days and number of ventilator days. The mean duration of steroid use was 7.64 for solumedrol and 6.5 for dexamethasone, which was in line with the recovery trial mean duration of 7 days [14]. We could not compare patients given intravenous hydrocortisone with REMAP-CAP study, as we had only 3 patients on hydrocortisone [25].

The morbidities were classified into sepsis, nephrological, pulmonary, hematological, cardiovascular and neurological complications. Overall, 22.6% of patients in SG developed morbidities, compared to 10.2% in SOC. As with previous secondary outcomes, this result was expected because patients presented with more severe conditions and had longer ICU and hospital stays. Approximately 14 different types of antibiotics were used; however, broad-spectrum restricted antibiotics, such as cefepime and meropenem, were used more in SG, indicating the physician's assessment of increased severity of this group.

Three antivirals were used, hydroxychloroquine sulfate, lopinavir + ritonavir, and favipiravir, whereas remdesivir was not used due to a lack of availability. Clexane was used as per the guidelines and Actemra was given infrequently. The aim of presenting this information was to shed light on the clinical practices used during the first wave of the pandemic.

Conclusion

There were some limitations to our study, namely the retrospective study design, small sample size, unevenly matched groups, heterogenous steroids used and the ongoing nature of the pandemic. All of these resulted in non-standardized, modified treatment protocols based on individual physicians' preferences. Many of the outcome measures could not achieve statistical significance, though there was a clear trend towards favorable outcomes from using steroids. There is adequate data to support the use of steroids in COVID-19 in large international trials, and our study presented us with results that favored the use of steroids. Our future studies will be aimed towards comparing treatment of COVID-19 patients during the first and subsequent waves of the pandemic. Due to much heterogeneity in the selection of steroids during the first wave, we hope to show the evolution of our treatment protocol in the subsequent waves of the pandemic.

References

1. United Nations [Internet] (2020) UN News; c2020 [cited 2020 Aug 01].
2. World Health Organization [Internet] (2020) WHO-China Joint Mission on Coronavirus Disease2019; c2020 [cited 2020 Feb 28].
3. Lazzerini M, Putoto G (2020) COVID-19 in Italy: momentous decisions and many uncertainties. Lancet Glob Health 8: e641-642.
4. World Health Organization. [Internet] (2020) Coronavirus disease 2019 (COVID-19): situationreport, 52; [cited 2020 Mar 12].
5. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, et. al., (2020) Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 369:m1985.
6. Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, et al., (2020) Should we stimulate orsuppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev 19:102567.
7. Channappanavar R, Perlman S (2017) Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 39:529-539.
8. Fehr AR, Channappanavar R, Perlman S (2017) Middle East respiratory syndrome: emergence of a pathogenic human coronavirus. Annu Rev Med 68:387-99.
9. Chen G, Wu D, Guo W, Cao Y, Huang D, et al., (2020) Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 130:2620-2629.
10. Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 46:846-848.
11. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, et al., (2020) Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis 20:1135-1140.
12. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, et al., (2016) Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315:788-800.
13. Wu C, Chen X, Cai Y, Zhou X, Xu S, et al., (2020) Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 180:934-943.
14. Chappell L, Horby P, Lim WS, Emberson JR, Mafham M, et al., (2021) Dexamethasone in hospitalized patients with Covid-19-preliminary report. N Engl J Med 384:693-704.
15. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, et al., (2005) Incidence and outcomes of acute lung injury. N Engl J Med 353:1685-1693.
16. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, et al., (2017) Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med 43:1751-1763.
17. Meduri GU, Siemieniuk RA, Ness RA, Seyler SJ (2018) Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS J Intensive Care 6:53.
18. Ni YN, Chen G, Sun J, Liang BM, Liang ZA (2019) The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care 23:99.
19. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, et al., (2020) Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 8:267-276.
20. World Health Organization (2020) Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. World Health Organization; 2020.
21. Russell CD, Millar JE, Baillie JK (2020) Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 395(10223):473-475.
22. Corral L, Bahamonde A, delas Revillas FA, Gomez-Barquero J, et al., (2020) GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. MedRxiv 2020.
23. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, et al., (2020) Early short-course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 71:2114-2120.

24. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, et al. (2020) Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA 324:1307-1316.

25. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, et al., (2020) Effect of Hydrocortisone on Mortality and Organ Support in Patients with Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA 324:1317-1329.

26. Force AD, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson N, et al., (2012) acute respiratory distress syndrome: the Berlin Definition. JAMA 307(23):2526-2533.